PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GOODWIN PROCTER LLP
Attn. Greenhalgh, Duncan A.
Exchange Place
53 State Street
Boston, MA 02109
UNITED STATES OF AMERICA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference RIB-028PC	Date of mailing *(day/month/year)* 24/11/2005
International application No. PCT/US2004/024334	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant RIB-X PHARMACEUTICALS, INC.	International filing date *(day/month/year)* 28/07/2004

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Eva Brell

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
RIB-028PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/024334	28/07/2004	29/07/2003
Applicant		
RIB-X PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box II).

3. [X] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/20 C07D413/06 C07D413/12 A61K31/421 A61K31/422

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 694 543 A (BAYER AG) 31 January 1996 (1996-01-31) page 91 - page 94; claim 1 page 83; examples 124,125 page 2, line 3 - line 4	1-8, 10-17, 20-23, 26-45
Y	EP 0 352 781 A (E.I. DU PONT DE NEMOURS AND COMPANY) 31 January 1990 (1990-01-31) page 51 - page 54; claim 1 page 2, line 4 - line 6	1-8, 10-17, 20-23, 26-45

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2005	24. 11. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRICKNER S J: "OXAZOLIDINONE ANTIBACTERIAL AGENTS" CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, NL, vol. 2, 1996, pages 175-194, XP001007528 ISSN: 1381-6128 the whole document; in particular, page 187, Figure (2); and page 189, column 2, last paragraph - page 190, column 2, Table IX	1-8, 10-17, 20-23, 26-45
A	WO 01/94342 A (DONG A PHARM. CO., LTD; LEE, JAE-GUL; LEEM, WON-BIN; CHO, JONG-HWAN; C) 13 December 2001 (2001-12-13) page 163 - page 170; claim 1 page 107; example 80 page 98; example 63 page 1, paragraph 1	1-8, 10-17, 20-23, 26-45
X	WO 01/81350 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY; BE) 1 November 2001 (2001-11-01) page 127 - page 134; claim 1 page 139; claim 12	1-8,12, 14,16, 20,22, 26-34, 41-43
E	WO 2005/012271 A (RIB-X PHARMACEUTICALS, INC; WU, YUSHENG; CHEN, SHILI; CHEN, YI; HANSEL) 10 February 2005 (2005-02-10) page 66 - page 68; examples 6,7; compounds 66,67 page 75 - page 78; example 13; compounds 155,156	1-6,8, 10,11, 13-17, 26-30, 32-45
E	WO 2005/019211 A (RIB-X PHARMACEUTICALS, INC; ZHOU, JIACHENG; BHATTACHARJEE, ASHOKE; CHE) 3 March 2005 (2005-03-03) page 173 - page 176; example 13; compounds 96,97 page 192; example 27; compound 127 page 217 - page 219; example 54; compound 402	1-6,8, 10,11, 13-17, 30,32-45

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Present claims 1-45 relate to "prodrugs" of the compounds of the present general formula.
The term "prodrug" is considered to lead to a lack of clarity within the meaning of Article 6 PCT because this term does not comprise any information as regards the structure of the compounds concerned. It is therefore impossible to compare the said "prodrug" compounds with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the said "prodrugs" have not been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8 (all partly), 10-15 (all partly), 16, 17, 20 (partly), 21 (partly), 22, 23 and 26-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-oxazolidin-3-yl group and A and B are phenyl;

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2. claims: 1-4 (all partly), 8 (partly), 10-13 (partly) and 26-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-oxazolidin-3-yl group, A is phenyl, B is selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, X is -NR4-, and M is other than formyl and C1-4acyl;

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3. claims: 1-4 (all partly), 8 (partly), 10-13 (partly), 26-29 (all partly) and 32-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-oxazolidin-3-yl group, A is phenyl, B is selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, and X is -NR4NR4-;

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4. claims: 1-4 (all partly), 8 (partly), 10-13 (partly), 26-29 (all partly) and 32-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-oxazolidin-3-yl group, A is phenyl, B is selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, and X is -S-;

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5. claims: 1-7 (all partly), 9-15 (all partly), 18, 19, 20 (partly), 21 (partly), 24, 25 and 26-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-oxazolidin-3-yl group, A is selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, B is phenyl, and X is -NR4- or -NR4NR4-;

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6. claims: 1-7 (all partly), 9-15 (all partly), 18, 19, 20 (partly), 21 (partly), 24, 25, 26-29 (all partly) and 32-45 (all partly);

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-oxazolidin-3-yl group, A is selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, B is phenyl, and X is -S-, and M is other than acetyl;

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7. claims: 1 (partly), 4-12 (all partly) and 26-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 2-(R3-CH2)-5-oxo-isoxazolin-4-yl group;

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8. claims: 1 (partly), 4-12 (all partly) and 26-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-isoxazolin-3-yl group;

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9. claims: 1 (partly), 4-12 (all partly) and 26-45 (all partly);

the compounds of the present claim 1 wherein Het-CH2-R3 represents a 5-(R3-CH2)-2-oxo-5H-furan-3-yl group;

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0694543 A	31-01-1996	AU	699940 B2	17-12-1998
		AU	2498595 A	01-02-1996
		BG	99790 A	30-04-1996
		CA	2154025 A1	21-01-1996
		CN	1119647 A	03-04-1996
		CZ	9501872 A3	14-02-1996
		DE	4425612 A1	04-04-1996
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		HR	950408 A1	30-04-1997
		HU	75035 A2	28-03-1997
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		AU	3911589 A	01-02-1990
		CA	1337526 C	07-11-1995
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		NZ	230108 A	25-10-1991
		PT	91315 A	08-02-1990
		US	4948801 A	14-08-1990
		ZA	8905778 A	27-03-1991
WO 0194342 A	13-12-2001	AU	5889701 A	17-12-2001
		BR	0111280 A	10-06-2003
		CA	2411859 A1	13-12-2001
		CN	1433413 A	30-07-2003
		EP	1289984 A1	12-03-2003
		HU	0301562 A2	29-12-2003
		JP	2003535860 T	02-12-2003
		MX	PA02012045 A	15-10-2003
		NZ	522990 A	29-08-2003
		US	2003166620 A1	04-09-2003
WO 0181350 A	01-11-2001	AT	268778 T	15-06-2004
		AU	781784 B2	16-06-2005
		AU	4863601 A	07-11-2001
		BR	0110240 A	07-01-2003
		CA	2405349 A1	01-11-2001
		CN	1437603 A	20-08-2003
		CZ	20023527 A3	15-01-2003
		DE	60103754 D1	15-07-2004
		DE	60103754 T2	16-06-2005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0181350 A		DK 1286998 T3	06-09-2004
		EE 200200598 A	15-04-2004
		EP 1286998 A1	05-03-2003
		ES 2220759 T3	16-12-2004
		HK 1053114 A1	18-02-2005
		HU 0300416 A2	28-06-2003
		JP 2003531211 T	21-10-2003
		MX PA02010453 A	25-04-2003
		NO 20025091 A	09-12-2002
		NZ 521765 A	28-05-2004
		PL 358326 A1	09-08-2004
		PT 1286998 T	30-09-2004
		TR 200402261 T4	21-12-2004
		US 2003216373 A1	20-11-2003
		ZA 200208187 A	11-02-2004
WO 2005012271 A	10-02-2005	NONE	
WO 2005019211 A	03-03-2005	NONE	

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/024334	28.07.2004	29.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D263/20, C07D413/06, C07D413/12, A61K31/421, A61K31/422

Applicant
RIB-X PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/024334

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8 (all partly), 9, 10-17 (all partly), 18, 19, 20-23 (all partly), 24, 25, 26-45 (all partly)

because:

☒ the said international application, or the said claims Nos. 34-42 (as regards industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-8 (all partly), 9, 10-17 (all partly), 18, 19, 20-23 (all partly), 24, 25, 26-45 (all partly)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, dc not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/024334

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-8 (all partly), 10-15 (all partly), 16, 17, 20 (partly), 21 (partly), 22, 23 and 26-45 (all partly);

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8 (all partly), 10-17 (all partly), 20-23 (all partly), 26-45 (all partly)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8, 10-17, 20-23, 26-45
Industrial applicability (IA)	Yes:	Claims	1-8 (all partly), 10-17 (all partly), 20-23 (all partly), 26-33 (all partly), 43-45 (all partly)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

1. The present **claims 34-42** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to *industrial applicability* of the subject-matter of these claims.

[For the assessment of the aforesaid claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

2. The expression "prodrug" as used in the present claims is unclear in the sense of Article 6 PCT. This expression is a functional definition which does not comprise any information as regards the structure of the respective compounds.
It was therefore impossible to compare the said "prodrug" compounds with what is set out in the prior art.
Consequently, the Partial International Search Report (PISR) was incomplete with respect to the said "prodrugs".

3. As a result of a lack of unity (Rule 13 PCT), the PISR had to be limited to the compounds of the present claim 1 wherein

Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group, and
A and **B** are ***phenyl***

(see, the first invention as defined under **item IV** below).

4. As the PISR forms the basis for this Written Opinion, the following statement on the patentability of the present subject-matter (see, the **item V** below) may only be regarded to be complete with respect to the present **claims 1-8 (all partly)**, **10-17 (all partly)**, **20-23 (all partly)** and **26-45 (all partly)**.

In so far as the following Written Opinion refers to the present **claims 1-8**, **10-17**, **20-23** and **26-45**, it should only be taken to refer the ***searched*** scope of the said claims as defined hereinbefore (cf., the items 2 and 3 above).

Re Item IV.

The present application lacks unity within the meaning of Rule 13 PCT for the following reasons:

The document EP-A-0694543 (**D1**) discloses (cf., pages 91-94, claim 1) i.a. 3-{[4-(acylaminoalkyl)phenyl]-(pyridinyl/pyrazinyl/pyrimidinyl...etc.)}-5-(aminomethyl)-2-oxo-oxazolidines which are said to have *antibacterial* activity (see, page 2, lines 3-4).
More specifically **D1** discloses (see, page 83, the compounds of the examples 124 and 125) two compounds which are excluded from the present claim 1 by virtue of the present proviso (see, the last two compounds of the present proviso).

The document EP-A-0352781 (**D2**) discloses (cf., pages 51-54, claim 1) i.a.

3-[4'-(acyl*oxy*alkyl)-4-biphenyl]-5-(aminomethyl)-2-oxo-oxazolidine derivatives (cf., the definition of X = $-C(R^6)(R^{23})-O-C(=O)-R^8$ according to claim 1 of **D2**) which differ from the present compounds only in that they are 4'-(acyl*oxy*alkyl)-biphenyl derivatives rather than 4'-(acyl*amino*alkyl)- or 4'-(acyl*thio*alkyl)-biphenyl derivatives (cf., the definition of the present substituent group X).

These compounds are also said to have *antibacterial* activity (see, page 2, lines 4-6). More specifically, **D2** discloses (see, the example 29) the compound N-[3-(4-(4'-(1-(2-carboxyethylcarbonyl*oxy*)ethyll)phenyl)phenyl)-2-oxo-oxazolidin-5-ylmethyl] acetamide.

The document WO-A-01/94342 (**D4**) discloses (cf., pages 163-170, claim 1) i.a. N-{3-[4-[(acetylthioalkyl)pyridinyl]-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide derivatives which are also said to have *antibacterial* activity (see, page 1, first paragraph). More specifically **D4** discloses (see, page 107, the compound of the example 80) Tthe compound N-{3-[4-[2-(acetylthiomethyl)pyridin-4-yl]-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide which is also excluded from the present claim 1 by virtue of the present proviso (see, the first compound of the present proviso).

In the light of **D1**, **D2** and/or **D4** the **problem** underlying the present application resides in the provision of <u>further</u> (alternative) 2-oxo-oxazolidine derivatives which are useful as *antibacterial* agents.

Accordingly, the present application proposes the compounds of the present **claim 1** in order to **solve** the given problem.

The only ***structural feature*** discernible which is **common** to **all** of the compounds of the present claim 1 is the

3 (or 4) - [(-C(=W)-X-(C_{1-6}alkylene)-)A - B] - 5 (or 2) - ($-CH_2-$) - Het

moiety (wherein W, X, A, B and Het are as defined in the present claim 1).

The documents **D1** and **D4**, however, already teach compounds comprising the said *3 - [(-C(=W)-X-(C_{1-6}alkylene)-)A - B] - 5 - (-CH_2-) - Het* moiety (cf., (i) the compounds of the examples 124 and 125 of **D1** and (ii) the compound of the example 80 of **D4**) *for the* ***same use*** (*antibacterial*) as the compounds of the present application.

As the only structural feature which is common to all of the present compounds (i.e., the *3 - [(-C(=W)-X-(C_{1-6}alkylene)-)A - B] - 5 - (-CH_2-) - Het* group) is not novel (cf., **D1** and **D4**), it cannot represent the "special technical feature" within the meaning of Rules 13.1 and 13.2 PCT.

The present application thus relates to different solutions to the given technical problem (i.e., the provision of <u>further</u> 2-oxo-oxazolidine derivatives which are useful as *antibacterial* agents) which are not linked by a single general inventive concept as set forth in Rule 13 PCT).

Hence the International Searching Authority considers that the following **nine** separate inventions / groups of inventions are not so linked as to form a single general inventive concept:

1. the compounds of the present claim 1 wherein

   Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group, and

   A and **B** are ***phenyl***,

   which differ from

   (i) the prior art **D1** (cf., the compounds of the examples 124 and 125) only in that the substituent group **B** is a ***phenyl*** group rather than a *pyridinyl* group, and

   (ii) the prior art **D2** (cf., e.g. the compound of the examples 29) only in that th ey

are 4'-(acyl*amino*alkyl)- or 4'-(acyl*thio*alkyl)-biphenyl derivatives rather than 4'-(acyl

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(cf., the present **claims 1-8 (all partly)**, **10-15 (all partly)**, **16**, **17**, **20 (partly)**, **21 (partly)**, **22**, **23**, and **26-45 (all partly)**);

2. the compounds of the present claim 1 wherein
   Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group,
   A is ***phenyl***, **B** is selected from ***pyridyl***, ***pyrazinyl***, ***pyrimidinyl*** and ***pyridazinyl***,
   X is -NR^4-, and
   M is ***other than*** *formyl* and C_{1-4}*acyl*
   which differ from the specific compounds of their closest prior art **D1** (cf., the compounds of the examples 124 and 125) only in that the present substituent group **M** is ***other than*** *formyl* and C_{1-4}*acyl* (cf., the present **claims 1-4 (all partly)**, **8 (partly)**, **10-13 (all partly)**, and **26-45 (all partly)**);

3. the compounds of the present claim 1 wherein
   Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group,
   A is ***phenyl***, **B** is selected from ***pyridyl***, ***pyrazinyl***, ***pyrimidinyl*** and ***pyridazinyl***, and
   X is -NR^4NR^4-,
   which differ from their closest prior art **D1** (cf., the compounds of the examples 124 and

125) only in that the substituent group **X** is a ***-NR⁴NR⁴-*** group rather than a *-NR⁴-* group (cf., the present **claims 1-4 (all partly)**, **8 (partly)**, **10-13 (all partly)**, **26-29 (all partly)**, and **32-45 (all partly)**);

4. the compounds of the present claim 1 wherein
Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group,
A is ***phenyl***, **B** is selected from ***pyridyl***, ***pyrazinyl***, ***pyrimidinyl*** and ***pyridazinyl***, and
X is ***-S-***,
which differ from their closest prior art **D1** (cf., the compounds of the examples 124 and 125) only in that the substituent group **X** is ***-S-*** rather than *-NR⁴-* (cf., the present **claims 1-4 (all partly)**, **8 (partly)**, **10-13 (all partly)**, **26-29 (all partly)**, and **32-45 (all partly)**);

5. the compounds of the present claim 1 wherein
Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group,
A is selected from ***pyridyl***, ***pyrazinyl***, ***pyrimidinyl*** and ***pyridazinyl***, **B** is ***phenyl***, and
X is ***-NR⁴-*** or ***-NR⁴NR⁴-***,
which differ from their closest prior art **D4** (cf., the compounds of the examples 63 and 80) only in that the substituent group **X** is ***-NR⁴-*** or ***-NR⁴NR⁴-*** rather than *-O-* (cf., the example 63 of **D4**) or *-S-* (cf., the example 80 of **D4**) (cf., the present **claims 1-7 (all partly)**, **9-15 (all partly)**, **18**, **19**, **20 (partly)**, **21 (partly)**, **24**, **25**, and **26-45 (all partly)**);

6. the compounds of the present claim 1 wherein
Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group,
A is selected from ***pyridyl***, ***pyrazinyl***, ***pyrimidinyl*** and ***pyridazinyl***, **B** is ***phenyl***, and
X is ***-S-***, and
M is ***other than*** *acetyl*,
which differ from their closest prior art **D4** (cf., the compound of the example 80) only in that the present substituent group **M** is ***other than*** *acetyl* (cf., the present **claims 1-7 (all partly)**, **9-15 (all partly)**, **18**, **19**, **20 (partly)**, **21 (partly)**, **24**, **25**, **26-29 (all partly)**,

and **32-45 (all partly)**);

7. the compounds of the present claim 1 wherein

Het-CH_2-R^3 represents a 2-(R^3-CH_2)-***5-oxo-isoxazolin-4-yl*** group,

which differ from the prior art **D1**, **D2** and **D4** essentially in that they are ***5-oxo-isoxazoline*** derivatives rather than *2-oxo-oxazolidine* derivatives (cf., the present **claims 1 (partly)**, **4-12 (all partly)**, and **26-45 (all partly)**);

8. the compounds of the present claim 1 wherein

Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***isoxazolin-3-yl*** group,

which differ from the prior art **D1**, **D2** and **D4** essentially in that they are ***isoxazoline*** derivatives rather than *2-oxo-oxazolidine* derivatives (cf., the present **claims 1 (partly)**, **4-12 (all partly)**, and **26-45 (all partly)**);

9. the compounds of the present claim 1 wherein

Het-CH_2-R^3 represents a 5-(R^3-CH_2)-***2-oxo-5H-furan-3-yl*** group,

which differ from the prior art **D1**, **D2** and **D4** essentially in that they are ***2-oxo-furan*** derivatives rather than *2-oxo-oxazolidine* derivatives (cf., the present **claims 1 (partly)**, **4-12 (all partly)**, and **26-45 (all partly)**);

The different inventions / groups of inventions were formulated in the order chosen by the Applicant.

Having regard to the compounds of the prior art **D1** and **D4**, it is noted that it cannot be excluded that in the course of the examination procedure the subject-matter of the aforesaid **items 2** and **6** has to be further subdivided because of a continuing lack of unity (cf., (i) the compounds 124 and 125 of the prior art **D1** and the compounds of the aforesaid **invention 2**; and (ii) the compound 80 of the prior art **D4** and the compounds of the aforesaid **invention 6**).

Re Item V.

Reference is made to the following documents:

D1: ..... EP-A-0694543 (31 January 1996);
D2: ..... EP-A-0352781 (31 January 1990);
D3: ..... Current Pharmaceutical Design 2(2), 175-194 (1996);
D4: ..... WO-A-01/94342 (13 December 2001);
D5: ..... WO-A-01/81350 (01 November 2001);
D6: ..... WO-A-2005/012271 (***10 February 2005***);
D7: ..... WO-A-2005/019211 (***3 March 2005***);

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document.
If it later turns out that this is not correct, the documents **D6** and **D7** as cited in the ISR could become relevant.

1. NOVELTY (Article 33(2) PCT):

The subject-matter of the present **first invention** (see **item IV**.1 above: the compounds of the present claim 1 wherein **Het-CH_2-R^3** represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group, and **A** and **B** are ***phenyl***) appears to be novel over the present **claims 1-8** (**all partly**), **10-17** (**all partly**), **20-23** (**all partly**) and **26-45** (**all partly**):

The documents **D1** (cf., pages 91-94, claim 1) and **D4** (cf., pages 163-170, claim 1) describe e.g. 3-[4-phenyl-(*pyridinyl/pyrazinyl/pyrimidinyl*...etc.)]-2-oxo-oxazolidine (cf., **D1**) and 3-[4-(*pyridinyl* or *pyrimidinyl)*phenyl]-2-oxo-oxazolidine derivatives (cf., **D4**).
The 3-(***biphenyl***)-2-oxo-oxazolidine derivatives of the present **first invention** are thus novel over **D1** and **D4**.

The document **D2** discloses (cf., pages 51-54, claim 1) 3-[4'-(acyl*oxy*alkyl)-4-biphenyl]-2-oxo-oxazolidine derivatives (cf., the definition of X = -$C(R^6)(R^{23})$-O-C(=O)-R^8 according to claim 1 of **D2**).
Accordingly, the present 4'-(acyl***amino***alkyl)-, 4'-(acyl***hydrazino***alkyl)- or 4'-(acyl***thio***alkyl)-biphenyl derivatives (cf., the definition of the present substituent group X) are also novel over **D2**.

The present 5-(aminomethyl)-3-(biphenyl)-2-oxo-oxazolidine derivatives are furthermore novel over **D3** (cf., the compounds of the table VIII on page 190) on account of the present substituent group ***M-X-*** (cf., the present 3-[4'-(***acyl*** (*amino* / ***hydrazino*** / ***thio)*** alkyl)-4-biphenyl]-5-(acetylaminomethyl)-2-oxo-oxazolidine derivatives and the compounds of the table VIII of **D3**).

There is an overlap between the present compound **claims 1-8**, **12**, **14**, **16**, **20**, **22** and **26-32** and the compounds of claim 1 of **D5** (cf., the compounds of claim 1 of **D5** wherein Q is selected from Q1 and Q2 wherein T represents AR1 or AR2)
However, as the document **D5** does not specifically disclose 3-(***M-X-bi***phenyl)-2-oxo-oxazolidine derivatives, the corresponding compounds of the present claim 1 may be considered to represent a **novel selection** from the compounds of claim 1 of **D5**.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-8**, **10-17**, **20-23** and **26-45** does not involve an inventive step (Rule 65(1)(2) PCT):

The compounds of the present **first invention** (see **item IV**.1 above: the compounds of the present **claims 1-8**, **10-17**, **20-23** and **26-32** wherein **Het-CH_2-R^3** represents a 5-(R^3-CH_2)-***2-oxo-oxazolidin-3-yl*** group, and **A** and **B** are ***phenyl***) **differ** from

(i) the compounds of **D1** (cf., claim 1 and the compounds of the examples 124 and 125) essentially in that the substituent group **B** is a ***phenyl*** group rather than e.g. a *pyridinyl* group,

(ii) the compounds of **D2** (cf., claim 1 and the compound of the example 29) essentially in that they are 4'-(acyl***amino***alkyl)- or 4'-(acyl***thio***alkyl)-biphenyl derivatives rather than 4'-(acyl*oxy*alkyl)-biphenyl derivatives, and

(iii) the compounds of **D4** (cf., claim 1 and the compounds of the examples 63 and 80) essentially in that the substituent group **A** is a ***phenyl*** group rather than a *pyridinyl* group.

Moreover, the compounds of the present **claims 1** and **12** may be regarded to represent a (novel) selection from the compounds of claim 1 of **D5** (see, item 1 above).

In the light of **D1**, **D2**, **D4** and/or **D5** the **problem** underlying the present **first invention** resides in the provision of <u>further</u> (alternative) 2-oxo-oxazolidine derivatives which are useful as *antibacterial* agents.

Accordingly, the present application proposes the compounds of the present **claim 1** in order to **solve** the given problem.

In view of the close structural relationship between the compounds of the prior art **D1**, **D2**,

D4 and/or **D5** (see above) and having regard to the fact that the prior art compounds are also useful as *antibacterial* agents, it is considered that the compounds of the present **first invention** have to be regarded as obvious alternatives to the 2-oxa-oxazolidine compounds of the prior art:

Given the teaching of the prior art **D1**, **D2**, **D4** and/or **D5** it is considered that the compounds of the present **first invention** do not possess a **common structural feature** which would distinguish them from the known compounds of **D1**, **D2** and/or **D4** and which could be seen as an **essential structural modification** of the prior art compounds with respect to the technical problem to be solved by the present application.

[1. The 5-(aminomethyl)-3-(*biphenyl*)-2-oxo-oxazolidine *core structure* (cf., the present **claims 1-8, 10, 11, 13-17** and **20-23**) is known from **D2**.
2. The 5-(*triazol-1-yl*methyl)-3-(*biphenyl*)-2-oxo-oxazolidine derivatives (cf., the present **claims 1-8, 12, 14, 16, 20, 22** and **26-32**) are known from **D5**.
3. It is known from **D3** (cf., page 187, Figure 2) and **D5** (cf., the definitions of R^2 and R^3 according to claim 1 of **D5**) that the 3-phenyl group may have *one or two fluorine* substituents at its *3* and/or *5-position* (cf., the present **claims 1, 6, 7, 14-17** and **20-23**).
4. It is furthermore known from **D3** (cf., page 187, Figure 2; and page 189, column 2, last paragraph - page 189, column 2, first paragraph) and **D5** (cf., the "optionally substituted" AR1 and AR2 rings according to claim 1 of **D5**) that the distal phenyl ring may be further substituted (i.e., with *all kind* of substituent groups) (cf., the present **claims 1** and **26-32**).]

The skilled person would thus have expected that the claimed compounds are also useful as *antibacterial* agents.

Accordingly, in the absence of any shown unexpected effect the subject-matter of the present **first invention** appears to be obvious in the light of the prior art prior art **D1**, **D2**, **D4** and/or **D5**.

Consequently, it is considered that the compounds of the present **claims 1-8**, **10-17**, **20-23** and **26-32** do not involve an inventive step as set forth in Article 33(3) PCT.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-8**, **10-17**, **20-23**, **26-45** concerns chemical compounds, pharmaceutical compositions, a chemical process and a medical device and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

4.1. The documents **D1**, **D2**, **D4** and **D5** should have been cited (Rule 5.1(a)(ii) PCT).

4.2. Claim 32 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

4.3. Process claim 43 is unclear because it does not comprise any process features (Article 6 PCT; clarity)

4.4. The passage on page 5, last paragraph - referring to *N-oxide*, *N-hydroxy* and *N-alkoxy* derivatives of the present nitrogen containing compounds - creates an inconsistency between the claims and the description (the present claims do not comprise any information as regards these N-derivatives).
This inconsistency leads to a doubt concerning the extent of protection sought, thus rendering the claims unclear, contrary to Article 6 PCT.

4.5. The statements on pages 1 (cf., lines 3-4) and 66 (lines 1-8), concerning
(i) the incorporation of patent documents and scientific articles and
(ii) the scope of the present invention
are obviously irrelevant and unnecessary in the sense of Rule 9.1(iv) PCT.